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Contributions to the Histology and Histogenesis of Sarcoma of the Uterus

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HISTOLOGY AND HISTOGENESIS OF SARCOMA OF THE UTERUS.[1]

It is only comparatively recently that sarcoma of the uterus has been recognized as a distinct affection, the first cases having been described little more than thirty years ago. But the very abundant literature upon the subject bears evidence of the interest which it has aroused among gynecologists as well as pathologists. Unfortunately the great majority of the articles upon uterine sarcoma have been written almost exclusively from a clinical point of view, and have devoted very little attention to the pathological aspect of the affection; in many instances the diagnosis being made from the clinical history alone, without microscopical examination. The pathological articles, on the other hand, have usually had only a limited scope, and have generally been characterized by a lack of knowledge of the work done by others, the result being that many authors claim to have made discoveries for the first time which in reality had been described years before.

Before entering upon the main object of this article—the consideration of the transformation of myomata into sarcomata, and the description of several specimens from the museum of

[1] From Prof. H. Chiari's Pathological-Anatomical Institute in Prague. Translated by the author from his article appearing simultaneously in the Zeitschrift für Heilkunde, Bd. xv., Hefte 2 und 3.

the Pathological Institute in Prague—we shall endeavor to give a brief review of the present status of sarcoma of the uterus and bring together some of the scattered statements concerning its pathology. It is more than probable that some of the growths described by Lebert as fibroplastic tumors of the uterus were in reality sarcomata. There is absolutely no doubt that the tumors described by Hutchinson,[52] Callender,[11] West,[102] and Paget[63] as "recurrent fibroids" were sarcomata; and the careful microscopical examination in Callender's[11] case shows clearly that he had to deal with a spindle-cell sarcoma of the uterus with metastases in various parts of the body. The first case to be described as sarcoma of the uterus was a polypus, the size of a fist, which C. Mayer[55] exhibited before the Berlin Obstetrical Society in 1860, and upon which Virchow[97] made the pathological report. He was soon followed by Langenbeck,[51] who reported a case of inversion of a sarcomatous uterus. The affection, however, did not assume a definite position in pathology until the appearance of Virchow's[98] "Krankhafte Geschwülste" in 1865, in which he accurately described sarcoma of the endometrium and pointed out the possibility of the transformation of fibromata and myomata into sarcomata. In 1867 G. Veit[96] devoted a portion of a chapter in his work upon the diseases of women to the affection, and described three cases of his own, including one involving the cervix, the first on record. Beginning with the first volume of the *Archiv für Gynäkologie*, 1870, cases of sarcoma of the uterus were frequently described, and within the next five years nearly all the prominent gynecologists of Germany published cases of their own, among whom we may mention Gusserow,[26] Hegar,[30] Chrobak,[13] Spiegelberg,[90] Winckel,[104] Leopold,[52] Scanzoni,[81] Ahlfeld,[3] and Fehling.[18] Hegar's [30] article appeared in 1871 and was based upon nine cases. In it he distinguished between sarcoma of the endometrium and the uterine wall, and gave so good a description of their histology that the abundant literature of the past twenty years has added comparatively little to his excellent work. We shall not attempt to further review the literature of the subject, and would refer those interested to the recent article of Von Kahlden,[37] in which he refers to a considerable number of the reported cases.

Generally speaking, sarcoma of the uterus may be divided into two great groups: those affecting (1) its mucosa and (2) its

parenchyma. Under these two main divisions there are, of course, numerous subdivisions, upon which we shall only briefly touch.

Sarcoma of the Endometrium.—Sarcoma of the endometrium is the most frequent of all forms of uterine sarcoma, and is usually limited to the body of the uterus. When affecting the mucous lining of the cervical canal it assumes a characteristic form, which we shall consider separately further on. Of one hundred and forty-four fairly accurately described cases which we have collected from the literature, at least forty-four, or about one-third, were limited to the mucous membrane lining the corpus uteri; and no doubt a considerable number, which we could not include among them on account of uncertainty as to their origin, also belonged in this category.

Sarcoma of the endometrium occurs either as a diffuse infiltration of the mucosa or as circumscribed growths which tend to assume a polypoid form. The former variety is the more frequent and may involve varying areas of the interior of the uterus, and is usually situated at or near the fundus. It leads to marked thickening of the mucosa, which often assumes a villous or jagged appearance, bleeds readily, and often presents large, necrotic areas. In most cases the process remains limited to the mucosa and does not invade the muscularis to any great extent, while in other instances it rapidly invades the uterine wall and leads to its destruction. According to the amount of fibrous connective tissue which they contain, the growths present on section a perfectly homogeneous or a more or less striated appearance, and may vary in color from grayish-white to light pinkish. These growths are frequently so rich in blood vessels that they may be designated as hemorrhagic or telangiectatic sarcomata. Of course when there is marked necrosis the typical appearance disappears and gives place to a very soft, dark tissue which readily breaks down. When the growth assumes a polypoid form it not infrequently presents a markedly fibrous structure, and on casual examination may readily be mistaken for an ordinary "fibroid polypus."

Sarcoma of the Parenchyma of the Uterus.—Sarcoma of the parenchyma of the uterus likewise appears in two forms, diffuse and circumscribed, the latter being of far more frequent occurrence. Indeed, the former occurs so rarely that many authors

do not mention it at all. It is due to the growth of the cells about the blood vessels or to the proliferation of the connective-tissue cells between the muscle bundles.

The circumscribed form, generally speaking, bears a marked resemblance to the myomata and gives rise to roundish tumor masses of various size and consistence, sometimes quite hard and again very soft. They are usually quite well marked off from the surrounding uterine parenchyma, except when they have attained a very large size, but are not usually surrounded by a capsule. Like the myomata, they occur either singly or multiple, and may be situated in any part of the uterine wall and so be either subserous, interstitial, or submucous.

The interstitial and submucous sarcomata have a marked tendency to make their way toward the uterine cavity and there assume a polypoid form, so that it is frequently impossible to decide whether a given polypoid sarcoma arises primarily from the parenchyma or mucosa. This is even more difficult during life than at the autopsy table, for in some cases a small portion of an interstitial sarcoma may perforate into the uterine cavity and hang down into it as a polypus, as in the cases of Orthmann,[62] Schultze,[86] and Wyder,[107] so that during life they would in all probability be diagnosed as arising from the mucosa.

It accordingly becomes evident that a very considerable number of cases cannot be definitely classified as arising either from the mucosa or the parenchyma of the uterus, and can only be said to arise from the corpus uteri. And consequently the statistical statements as to the frequency of the various forms of uterine sarcoma are open to serious doubt. Of course there can be no doubt in the cases in which the growth is surrounded on all sides by uterine tissue or arises from the external surface of the uterus.

This form of uterine sarcoma, on section, presents a varying appearance, and may be either entirely homogeneous or contain large fibrous areas; the latter being of such frequent occurrence that these growths are generally spoken of as fibro- or myo-sarcomata, and are generally considered to be derived from the fibromyomata. Owing to necrotic changes they frequently present various colors and not infrequently cystic formations. Like the myomata, they may contain many dilated vessels and

so assume a telangiectatic form, as in the cases reported by Johannovsky,[34] Jacubusch,[33] and others; or may contain cysts of various sizes, the result of dilatation of the lymphatics, and thus give rise to lymphangiectatic sarcomata, which have been described by Fehling and Leopold[18] and Fenger.[19] And in some instances sarcomatous nodules may be found in the wall of a uterus whose endometrium is also sarcomatous, thus presenting a combination of the two forms.

Microscopically the uterine sarcomata do not differ greatly from sarcomata in other parts of the body, and may consist of round, spindle, or giant cells, or a mixture of the various forms.

It is generally stated that the round-cell sarcoma occurs most frequently; next in frequency is a mixture of round and spindle cells, while the pure spindle-cell sarcoma occurs comparatively rarely; and, as will be seen later, very little is said about giant-cell sarcomata.

It is interesting to note that several observers claim to have been the first to describe a pure spindle-cell sarcoma of the uterus. Thus, in 1874, both Leopold[62] and Grenser[25] stated that they were the first to observe such a case, and as late as 1890 Beissheim[7] made a similar claim, when in reality the case of Callender,[11] reported in 1857, was apparently the first of the kind to be recorded. Personally we have not been impressed with the great rarity of spindle-cell sarcoma of the uterus, and an analysis of the literature afforded us eighty-eight cases in which the form of the cells composing the growths was definitely described; of these, thirty-one were spindle-, twenty-seven round-, and thirty mixed-cell sarcomata. We do not wish to claim that these figures represent the relative frequency of the various forms of sarcoma of the uterus, and we only adduce them to demonstrate that the spindle-cell variety occurs more frequently than many writers suppose. We believe, however, that the round-cell variety is found most usually in sarcoma of the endometrium. We find here, as in sarcomata in other parts of the body, variations in the quantity of cells composing the growth, and in the arrangement of the intercellular tissue, which give rise to varying forms, which we designate as medullary, fibro-, and alveolar sarcoma.

Sarcoma of the Cervix.—It is generally stated that sarcoma of the cervix occurs but rarely, and we have met with only one

case in Baltimore, which we are unfortunately unable to report in this connection, as our records are not accessible at present. But we have been able to collect thirty-four cases from the literature in which the process was limited to the cervix, and several other cases in which both the cervix and body of the uterus were involved when the case was first seen. The cases of cervical sarcoma are readily divided into two groups, one of which appears to be very distinct, while the other, no doubt, includes several varieties of growths.

"*Grape-like*" *Sarcoma of the Cervix.*—From the mucous membrane of the cervical canal and the vaginal portion a growth may arise which closely resembles in appearance an hydatiform mole or myxomatous degeneration of the chorion.

Spiegelberg[91] was the first to direct attention to this class of growths, under the title, "Sarcoma colli uteri hydropicum papillare," when he described a case occurring in a 17-year-old girl, in whom he found the anterior lip of the cervix thickened and enlarged, and covered on its margin as well as its surface by a group of oval, yellowish-brown outgrowths, one to two centimetres long, which looked like transparent cysts, which were readily crushed when touched and contained a thick, sticky fluid. The anterior lip of the cervix was removed with scissors. Nine months later the girl returned with the entire vagina filled by a growth which resembled an hydatiform mole in appearance, which also arose from the anterior lip by numerous strong, thread-like pedicles. The mass was again removed and rapidly recurred; eventually the entire uterus was removed, and the patient died later from recurrence.

The tumors were examined by Weigert, who found that the cyst-like masses were covered by a single layer of cylindrical epithelium, and their interior composed of large round, spindle, and branching cells, which were separated from one another by clear spaces which were traversed by fine threads. In these spaces lymph corpuscles were found, and between the cells thin-walled blood vessels. In the more compact portions of the growth, and in the pedicles of the "cysts," large cells without the clear ground substance were seen. The growth at first suggested a myxomatous sarcoma, but fresh specimens failed to give the characteristic mucin reaction with acetic acid. Spiegelberg accordingly concluded that the appearance was due to edema

the result of stasis in the numerous lymph sinuses of the cervix and suggested for it the above-mentioned name.

The next year he reported a similar case,[92] and stated that one of his cases, which had been reported by Kunert,[49] was also of this variety. Similar cases were soon reported by several observers under various names. For example, Rein[70] described a case as "myxoma enchondromatodes arborescens colli uteri"; Pernice,[64] as "traubiges Myosarcoma striocellulare uteri"; and Mundé,[57] as "a rare case of adeno-myxo-sarcoma of the cervix."

Pfannenstiel[66] in 1892 reported a new case, and in his excellent monograph collected the previous cases and suggested for the group the neutral name of "grape-like" sarcoma ("das traubige Sarcom") of the cervix, under which the various cases could be classified and note taken of their peculiarities. He agrees with the majority of observers that the growths in question are not myxomata or myxo-sarcomata, and believes with Spiegelberg[91,92] and Weigert that they are sarcomata infiltrated with lymph and could be designated with propriety as "sarcoma lymphangiectaticum et hydropicum." He showed conclusively that the growth in his case arose from the superficial portions of the cervical mucous membrane, to whose papillary structure it owed its peculiar form; and in all probability that it was connected in its origin with proliferative changes, which he observed about the lymphatics and blood vessels.

Exclusive of his own case he found eleven other cases in the literature—namely, those described by Weber,[101] Kunert,[49] Kunitz,[50] two by Spiegelberg,[91,92] Rein,[70] Thomas,[95] Winckler[106] (Sänger), Pernice,[64] Mundé,[57] and Kleinschmidt.[44] We do not believe that the case of Kleinschmidt[44] should be reckoned among the "grape-like" sarcomata (*traubige Sarcomata*), for in its description he failed to mention that it had the appearance which is so characteristic of this form of growths, and he classed it himself among the angio-sarcomata. It is also doubtful whether the case described by Winckel[105] as an "adeno-myxo-sarcoma cervicis" belongs in this category.

On the other hand, it is quite certain that a specimen which Byford[10] obtained by vaginal hysterectomy in a woman aged 57 should be classed among the "grape-like" sarcomata of the cervix, and more than probable that the cases described by

Ahlfeld[2] and Smith[89] in girls, respectively, 15 and 3 years of age also belong in the same group.

It is interesting to note that glandular structures were found in the cases of Mundé,[67] Winckel,[105] and Byford,[10] and that hyaline cartilage was found in the cases of Rein,[70] Pernice,[64] Kleinschmidt,[44] and Pfannenstiel,[66] and striated muscle in those of Weber,[101] Kunert,[49] and Pernice.[61] The presence of cartilage and striated muscle in these growths is of great interest in connection with their histogenesis; and, unless we accept the theories of Weber and Pfannenstiel, who regard them as the result of metaplasia of the sarcoma cells, they would appear to us to indicate a *vitium primæ formationis* (*Keimverlagerung*) in Cohnheim's sense.

It is also interesting to note that the great majority of these cases occurred in persons under 20 years of age or past the menopause, and only three in the intermediate period; and also that they all died from regionary metastases, with the exception of Byford's[10] patient, of whom it is only stated that she recovered from the operation; and that true metastases occurred only in the cases of Kunert[49] and Kunitz.[50]

Other Forms of Sarcoma of the Cervix.—Besides this well-defined group of "grape-like" sarcomata, we have found eighteen other cases in the literature in which there is no doubt that the affection arose primarily from some portion of the cervix, either from its parenchyma, or from the mucosa lining its canal, or from the submucosa of the vaginal portion. From the description of the cases it is not always evident from which structure they originated, but it is apparent that they do not constitute so definite a group of tumors as those just mentioned. Thus, for example, we find five cases in which it was said that the growth arose from the cervical canal with a broad basis, and usually from its mucosa—namely, those of Leopold,[52] Hunter,[31] Dressler,[16] and two of Kaltenbach.[38] The cases of Veit,[96] Hackeling,[29] Beermann,[5] Johnston,[35] and Bommer[9] had a polypoid form, were attached by a pedicle to some part of the cervical canal, and usually protruded into the vagina with the pedicle passing through the os externum. In Scanzoni's[81] case the sarcoma arose from the anterior lip of the cervix, those of Kleinschmidt[44] and Rosthorn[76] from the posterior lip, and the two cases reported by Bommer[9] arose from both lips.

The cases of Grenser[25] and Zweifel[109] presumably arose from the exterior of the cervix, and we are unable to give any particulars as to the case mentioned by Rogivue[74] on account of its meagre description. The microscopical examination of the various tumors makes their diversity even more apparent than their macroscopical appearance. Thus the specimens of Hackeling[29] and Johnston[35] contained glandular elements, and the latter was also said to be a melano-sarcoma. Leopold stated[52] that his tumor was originally a fibroma which had become sarcomatous. Kleinschmidt's[44] specimen was a spindle-cell angiosarcoma, while those of Grenser[25] and Zweifel[109] were spindle- and round-cell sarcomata respectively; and in Rosthorn's case it was clearly shown that the primary growth arose from the submucosa of the vaginal portion.

Besides the varieties of sarcoma to which we have already referred, there are a considerable number of cases on record which are described as combinations of sarcoma with other tumor formations—as adeno-, carcino-, chondro-, and osteo-sarcoma.

Adeno-sarcoma.—When considering the "grape-like" sarcomata of the cervix we mentioned that several of the cases had been described as adeno-sarcomata; but it is evident that the presence of glandular structures in them is due only to the persistence of some of the original glands of the cervical mucous membrane, and therefore is of no great importance and does not entitle them to a separate classification.

On the other hand, Schmitt[83] and Kay[40] have described cases of adeno-sarcoma of the body of the uterus in which glandular structures were observed in the sarcomatous endometrium. From the description of their specimens it appears that they had only to deal with more or less normal uterine glands which had not yet been destroyed by the sarcomatous new growth; and Schmitt[83] said of his two cases that "the glands were scarcely increased in number," which appears to us to be sufficient evidence that he did not have to deal with true adenomatous growth.

Carcino-sarcoma.—We cannot dispose of the carcino-sarcomata with the same ease, for their existence is vouched for by Virchow,[98] Gusserow,[27] Klebs,[42] and others.

In his "Geschwülste" Virchow[98] stated, without giving any particulars, that he had seen several cases, and that they were

far more malignant than the ordinary varieties of uterine sarcoma; and lately, in the discussion upon the work of Abel and Landau,[1] he reaffirmed his belief in the existence of this class of tumors. Klebs[42] also stated that they were of frequent occurrence, and Gusserow[27] said: "If the existence of a certain relationship between the round fibrosarcoma of the uterus and cancerous formations (*Krebsentwickelung*) cannot be denied, it is so much more frequent and marked in the second form of sarcoma of the uterus (sarcoma of the endometrium) that it has become doubtful whether one is justified in regarding it as a particular variety of tumor formation."

Cases of so-called carcino-sarcoma have also been described by Rabl-Rückhardt,[68] Rosenstein,[75] and Keller,[41] but it is not at all evident from the descriptions of Rabl-Rückhardt[68] and Rosenstein[75] that they had to deal with sarcomata; Rabl-Rückhardt's case, upon which Gusserow appears to base his belief in this class of tumors, being apparently a carcinoma of the corpus uteri which had grown down into a submucous myoma. In Keller's[41] case a tumor the size of a walnut arose from the posterior wall of the uterus, near the mouth of the right tube, which he stated presented a combination of a round- and spindle-cell sarcoma with a carcinoma. This he regarded as a "secondary metaplasia" of a mixed submucous polypus, in which the carcinoma arose from the glands and the sarcoma from the interglandular tissue. We should hesitate to regard this case as a carcino-sarcoma; and it is evident that the term is as inapplicable to Rabl-Rückhardt's[68] case, admitting that it was a sarcoma, as the term carcino-fibroma or myoma would be to the not very infrequent cases in which carcinomata of the corpus invade fibromyomata which are situated in its walls. It is not improbable that some of the so-called carcino-sarcomata of Virchow,[97] Klebs,[42] and others were decidual-cell sarcomata (deciduoma malignum); and Keller[41] states that in three instances he has mistaken diffuse carcinoma of the endometrium for sarcoma, and Orth[50] says that endotheliomata of the uterus may assume an adenomatous form and readily be mistaken for carcinomata.

None of us who believe in the purely epithelial origin of carcinoma can admit the existence of transition forms between sarcoma and carcinoma, or *vice versa*. Nor do we believe that

the so-called "sarcomatous degeneration" of the endometrium of Abel and Landau[1] represents the initial stage in the development of carcinoma of the body of the uterus, or that it results from the same cause which produces the carcinoma of the cervix.

Chondro-sarcoma.—Chondro- and osteo-sarcomata may be the result of further changes on the part of the connective-tissue elements of the sarcoma (metaplasia), as well as accidental complications (*vitium primæ formationis*).

A case described by E. Wagner[99] as an enchondroma of the uterus in all probability was a chondro-sarcoma. It occurred in a woman, aged 55, whose uterus measured 5, 3.5, 3.5 inches in its several diameters. When cut open it resembled a thin-walled cyst, from whose inner surface many villous structures and nodular ridges arose. These portions creaked on section, and under the microscope "consisted of fibres and homogeneous bundles, which in many places went over into areas of hyaline cartilage. Between the fibrous bundles were many connective-tissue elements, spindle- and star-shaped," many of them being very fatty. The growth contained very few vessels. In each lung there were about fifteen nodules, which varied from a pea to a walnut in size and presented the same structure as the uterine tumor.

Geissler[22] also observed areas of hyaline cartilage in a spindle- and round-cell sarcoma of the endometrium which arose from the posterior and lateral wall of the uterus in a woman 50 years old, and which gave rise to a tumor about 2.5 centimetres in diameter; and when considering the "grape-like" sarcomata of the cervix we stated that areas of hyaline cartilage had been found in the cases of Rein,[70] Pernice,[64] Kleinschmidt,[44] and Pfannenstiel.[66]

As far as we can learn, no one has as yet reported an undoubted case of *osteo-sarcoma* of the uterus, the case reported by Newton[58] under that name being merely a calcified subperitoneal fibromyoma which arose from the fundus of the uterus, weighed twenty-two pounds, and had existed for twenty-five years.

Up to the present it appears uncertain whether a case of true *melano-sarcoma* of the uterus has ever been reported, and for

the scanty references in the literature to this form of sarcoma we would refer to the remarks which follow our Case 3.

Sarcoma deciduo-cellulare.—During the past few years another variety of sarcoma has been added to the various forms which may affect the uterus, under the name of deciduoma malignum, or sarcoma deciduo-cellulare. This, which is the most malignant of all forms of uterine sarcoma, was brought to the attention of the profession by Sänger [78] and Pfeifer,[67] a pupil of Chiari, each describing a case. The cases were published within a short time of each other, but totally independently, Sänger's article appearing first. Both described similar cases, and both proposed to call them deciduoma malignum.

In Sänger's [78] case a healthy young woman, 23 years old, had an incomplete abortion in the eighth week. She bled for four weeks after it, and when Sänger saw her she presented the symptoms of resorptive fever. The uterus was cleaned out and the hemorrhage ceased, but she did not regain her health. The uterus gradually increased in size, and soon a tumor appeared in the right iliac fossa. She developed cough, shortness of breath, became greatly emaciated, and died seven months after the abortion. At autopsy the uterus was found to be as large as if three to four months pregnant, and its walls occupied by four tumor masses of dark-red color and hemorrhagic consistence, the largest being five to six centimetres in diameter. The endometrium did not appear to be involved. There were metastases, of the same character as the original tumor, in the lungs, diaphragm, iliac fossa, and the tenth rib on the right side.

The microscopical examination showed that the metastases, as well as the original uterine tumors, were made up of areas of large epithelioid cells, which closely resembled decidual cells, and which were separated from similar areas by areas of hemorrhage. The cells themselves were separated by a fine reticulum. Throughout the specimen there were a large number of open spaces and many giant cells, so that it corresponded very closely in structure to the stratum spongiosum of the decidua. In some places these cells could be seen along the sides of the vessels and apparently taking the place of their endothelium, though it was impossible to decide whether they were derived from it or not. This relation of the growth to the vessels readily explained its hemorrhagic appearance as well as the

rapid formation of metastases. From the study of his case Sänger had no hesitation in considering it due to an abnormal proliferation of the decidual cells.

Pfeifer's[67] case was almost exactly similar, the woman dying five months after the first hemorrhage, with cough, emaciation, etc. From the posterior wall of the uterus a growth the size of a fist arose, which had the same appearance and microscopical structure as in Sänger's case. There were also metastases of a similar character in the lungs and vagina. Pfeifer at first believed that he had to deal with a carcinoma, but the discovery of a reticulum between the cells, and its general resemblance to the decidua, soon led him to recognize its true character and propose to call it a deciduoma malignum. Upon examining the specimen in Pfeifer's case Chiari immediately stated that three cases which he had described in 1877[12] as primary carcinoma of the uterus developing after the puerperium, with regionary and pulmonary metastases, were exactly similar, and that he had no hesitation in grouping the four cases together as malignant deciduomata.

At the Breslau meeting of the German Gynecological Society (1891) Sänger[79] read a paper upon this subject, and very properly showed that the term deciduoma malignum had not been happily chosen, and proposed instead to designate this form of growth as sarcoma deciduo-cellulare and thus give it its proper place among the sarcomata. In the discussion which followed P. Müller[56] reported another case without autopsy; and within the past year a number of cases have been reported by Gottschalk,[24] Köttnitz,[46] two by Schmorl,[64] and one by Löhlein.[53] In the cases of Köttnitz,[46] Gottschalk,[24] and Löhlein[53] the diagnosis of deciduoma malignum was made *intra vitam*, and the uterus removed in the last two cases. Gottschalk's[24] patient, however, died seven months later with hemorrhagic metastases in various parts of the body, and up to the present Löhlein's[53] patient appears to be the only one who has not died from the affection.

In the cases of Gottschalk,[24] Köttnitz,[46] and one of Schmorl,[64] besides the typical decidual character of the growths, there also appears to be a sarcomatous change in the chorionic villi, which they consider the initial change, and from which they suppose the rest of the uterus is infected. Gottschalk[24] proposed to call his case a sarcoma chorion-deciduo-cellulare; while Schmorl[64]

considers that they are closely related to the "destruirende Placentarpolypen" of Von Kahlden,[36] Zahn, and others, and is doubtful whether they can be properly designated as sarcomata, and consequently proposes to designate the entire group as "blastoma chorion-deciduo cellulare." It would lead us too far, however, to attempt to discuss the many aspects of this variety of uterine sarcoma, and for their consideration we would refer those interested to Sänger's[50] recent monograph upon the subject. There is no doubt that many cases of so-called hemorrhagic sarcoma belong in this category, and we have no hesitation in saying that Jacubusch's fourth case, and one described by Guttenplan as sarcoma hemorrhagicum, should also undoubtedly be classed among them. There is also but little doubt that some of the other cases of carcinoma of the body of the uterus, as well as those of Chiari,[12] belong in this group; and, as we have already hinted, it is more than probable that some of the so-called carcino-sarcomata also belong in this category. When we consider the marked uniformity of the clinical history as well as the anatomical conditions in these cases, we must feel that we have to deal with the most interesting as well as the most malignant of the uterine sarcomata.

Metastases.—It is generally stated that metastases occur but rarely in the course of sarcoma of the uterus; and we may say that their occurrence is not general, death usually resulting from exhaustion rather than from the formation of metastases.

With one exception, as stated above, every case of decidual-cell sarcoma has proved rapidly fatal, and in every instance hemorrhagic metastases were found in the lungs and frequently in the vagina and other organs. In addition to the eleven cases of decidual-cell sarcoma we have found twenty-three other cases in the literature, including two cases of our own, in which true metastases were found at the autopsy; in nearly every case they were situated in the lungs and frequently in other organs, and in only two or three instances in the lymphatic glands.

The occurrence of metastases in organs far distant from the uterus, without involvement of the lymphatic glands, can only be explained by infection through the blood. Ample proof for this mode of origin is afforded by the cases of decidual-cell sarcoma of Sänger[78] and Pfeifer,[67] the cases which Pestalozza[65] calls infectious hemorrhagic sarcoma, and the angio-sarcomata described by Kleinschmidt[44] and Von Kahlden,[37] for in all of

them sarcoma cells and tumor masses were observed within vessels which were apparently venous; and also by the cases of Katz[39] and Geissler,[22] in which the pelvic veins were found filled by sarcomatous thrombi. In Katz's[39] case definite sarcomatous thrombi were found in the pulmonary arteries, which gave rise to pulmonary metastases; while in Geissler's[22] case the process was still limited to the pelvic veins and had not yet led to their formation. These observations serve to demonstrate that Zenker's[108] statement, that most sarcoma metastases are due to infection by the blood, applies as well to the uterus as to the other organs. The vaginal metastases which occur so frequently in the cases of decidual-cell sarcoma are far more difficult of explanation, and their mode of origin is still an open question.

Other Complications of Sarcoma of the Uterus.—Besides the formation of metastases, sarcoma of the uterus may give rise to several other complications, several of which are of interest and deserve a brief mention.

In several instances the sarcomatous new growths have perforated the uterine wall, thus allowing its necrotic contents to escape into the peritoneal cavity. This was noted in cases of Weber[101] and Dressler,[16] in which death resulted from acute peritonitis; and in the case of Jacubusch,[33] which we have included among the decidual-cell sarcomata, death was due to hemorrhage from the rupture of a nodule on the posterior wall of the uterus. In the cases of Finlay[20] and Reunert,[71] the uterine growth perforated into the intestines; and in the cases of Gusserow[26] and Ritter[73] abscesses followed the perforation into the peritoneal cavity, which in turn ruptured through the abdominal wall. In several cases of sarcoma of the endometrium the internal os has become clogged up, thus preventing the escape of the contents of the uterus and so leading to the formation of a pyometra; this was noted in cases of Freund,[21] Terillon,[93] and Kay,[40] and in our Case 3. In Terillon's[93] case the uterus contained seven litres of thick, dark fluid, and he mentioned a case of Péan in which the uterus contained fifteen litres of fluid. In several cases of sarcoma of the endometrium inversion of the uterus has been observed; this was noted in cases of Wilks,[103] Langenbeck,[51] Spiegelberg,[90] Simpson,[88] and Beissheim,[7] and in most instances was mistaken for a sarcomatous polypus, whose removal was attempted with fatal result.

It is interesting to note that the cases of Spiegelberg [90] and Simpson [85] occurred in nulliparous women, among whom inversion of the uterus is practically unknown; and Simpson [88] attributed it to loss of tone of the uterine musculature, resulting from its invasion by the sarcomatous new growth; and, lastly, in the cases of sarcoma of the endometrium described by Simpson [88] and Coleman [14] the process had extended directly into the tubes, the submucous tissue being the first to become affected.

Histogenesis.—The consideration of the histogenesis of sarcoma of the uterus will be simplified if we consider separately the forms occurring in its endometrium and parenchyma.

The comparatively simple structure of the mucous membrane of the uterus renders it evident that sarcoma of the endometrium can have only two sources of origin—namely, from the interglandular tissue and the vessel walls. There is no doubt that the great majority of sarcomata of the endometrium are developed directly from its connective-tissue cells; and it is only necessary to recall the histological appearance of some forms of interstitial endometritis to understand what a slight histological difference exists between the malignant and benign forms of proliferation of the connective tissue of the endometrium.

In a certain number of cases, however, the growth may originate by proliferative processes about the vessels. Indeed, Waldeyer [100] considers it the usual mode of origin for sarcoma in general, and it likewise undoubtedly applies to a certain proportion of cases of sarcoma of the endometrium. Pfannenstiel [66] is as yet the only observer to demonstrate this, though Amann [4] has recorded a case of endothelioma of the vaginal portion of the cervix which arose from the lymph channels in the lower layers of its mucous membrane.

As shown by Keller [41] and Von Kahlden,[37] sarcomata may originate in the lower layers of the endometrium and for a long time leave its superficial layers more or less intact, so that the entire surface of the growth may be covered by tissue containing glands.

The decidual-cell sarcomata likewise originate in the mucosa, but the consideration of their histogenesis would necessitate the discussion of the origin of the decidual cells themselves; and as those who have busied themselves with the study of the placenta have not yet decided whether they arise entirely from the connective-tissue cells or also in part from the vessel walls, we must leave their consideration to others.

As we have already stated, a large number of authors suppose that sarcoma of the parenchyma of the uterus is always the result of secondary changes in uterine myomata. Most writers upon sarcoma of the uterus have accepted this doctrine without hesitation, and consequently have entirely overlooked other modes of origin; and even those who have not accepted it in its entirety believe that it is the most frequent mode of origin, while the development of sarcoma from the normal constituents of the uterine wall is the exception. There is, however, no doubt that sarcomata may arise from the interstitial connective tissue and the blood vessels of the uterine wall, in which there is no sign of fibromyomatous formations.

As far as we can learn, Eppinger[17] is the only observer who has described sarcomata arising from the interstitial connective tissue of the uterine wall. In his case there were sarcomatous nodules of considerable size in the walls of the uterus, which he demonstrated were due to the proliferation of the interstitial connective tissue and the adventitia of the vessels.

Beermann[5] and Klebs[42] both state that sarcomata of the uterine wall may also arise from the blood vessels, but fail to give any histological details. The first actual proof for this mode of origin was adduced by Kleinschmidt,[44] who described an angio-sarcoma of the cervix, to which we have already referred. A soft, nodular tumor, the size of an orange, arose from the posterior lip of the cervix, which was removed and cauterized; recurrence two months later. It soon attained the same size and was once more removed. The microscopical examination showed that both tumors presented the same structure and were made up of large spindle cells arranged parallel to the vessels. He then says: "The sarcoma appears to arise from the blood and lymph vessels, which are very abundant in both tumors. Generally it appears to originate from the adventitia of the vessels, but in many places a distinct proliferation of the intima can also be observed, generally forming an opaque, tolerably broad, almost homogeneous layer about the vessel. In many places nothing more can be seen of the real vessel wall, as it is completely transformed into sarcomatous tissue."

Two years later (1893) Von Kahlden[37] also described a case of angio-sarcoma affecting the body of the uterus as well as the cervix, in which this mode of origin was also clearly demonstrated. The growths were composed of oval cells, which were

arranged concentrically about the vessels, thus forming small nodules, which by their coalescence gave rise to larger ones. He claims that he is the first to have observed such a case, and completely ignores the claims of Kleinschmidt's[44] case in this regard, of which he says: "The microscopical examination revealed a sarcoma, very rich in blood vessels, which was composed of spindle cells thickly crowded together." Orth[60] also states "that there are also sarcomatous tumors which resemble the carcinomata very closely, particularly certain adenomatous forms, but which must be classed among the sarcomata, as they are new growths which are due to a proliferation of the endothelium of the blood vessels, and accordingly must be designated as endotheliomata." There is also no doubt that sarcoma-like growths may be derived from the muscle cells themselves, as was stated by Beissheim[7] and Pestalozza.[65] We shall, however, defer the consideration of this mode of origin until after the consideration of our Case 1.

The transformation of fibromata and fibromyomata into sarcomata, or their "sarcomatous degeneration," as most authors insist upon calling it, has long been a favorite theme with those who have busied themselves with the consideration of uterine sarcomata; and a very large number of authors do not hesitate to state that it occurs very frequently, and indeed is the most usual, if not the only, mode of origin for sarcoma of the parenchyma of the uterus. But, unfortunately, most of the arguments in favor of this mode of origin are based entirely upon clinical grounds or upon the mere macroscopical appearance of the tumors. It is generally believed, if a "fibroid growth" be removed from the uterus and be soon followed by another, that the second is necessarily a recurrence of the first, and such cases are generally regarded, without an attempt at microscopical examination, as conclusively demonstrating the malignant character of the growth and the transformation of a fibromyoma into a sarcoma; while the more natural explanation is that they are frequently totally independent of each other and the apparent recurrence is only a coincidence. In this connection it must be remembered that cases have been recorded by Klebs,[43] Krische,[47] and Orth[60] which tend to show that fibromyomata may recur in very rare instances, and even give rise to metastases, and still present absolutely no sign of being sarcomatous. Such observations, though extremely rare, show the

great need of caution in drawing conclusions in these cases, and demonstrate the absolute necessity of the microscopical demonstration of the sarcomatous nature of the growths before basing any arguments upon them. In some instances even the microscopical examination does not render an infallible verdict, as was demonstrated by a case in which Winckel [104] removed, in the course of a little more than two years, three tumors from the interior of the uterus, the first of which he regarded as a fibroma and the other two as round-cell sarcomata which were due to the "sarcomatous degeneration" of the base of the first. Two years later Schatz [82] removed a fourth tumor from the same patient, which he demonstrated was only an inflamed myoma, and clearly showed that Winckel [104] had regarded similar tumors as sarcomata. The subsequent history of the case demonstrated the correctness of Schatz's [82] verdict, for the woman was perfectly well three years after the removal of the third "recurrence."

Most of the authors who attempt to demonstrate this transformation by means of the microscope fail to show anything more than sarcomatous tissue adjoining myomatous. But, in our judgment, no one has as yet conclusively demonstrated the histological stages in this transition (*Uebergang*). It cannot be denied, however, that there is a great deal to be said in favor of its occurrence, and we do not care to be understood as attempting to throw doubt upon it, and in the remarks which follow we shall endeavor to prove that it does occur; but, in view of what has already been said, it is evident that it does not constitute the universal mode of origin for sarcoma of the parenchyma of the uterus.

The macroscopical resemblance of many uterine sarcomata to the ordinary "fibroid polypi" early suggested to the English observers that they were closely related to one another, and in designating them as "recurrent fibroids" they gave evidence of this belief; but since the demonstration of their sarcomatous nature the term has gradually fallen into disuse.

Virchow,[98] in his "Geschwülste," stated the possibility of the transformation of fibromata and myomata into sarcomata, and most of the earlier writers readily accepted his statement. Hegar,[30] Leopold,[52] and Chrobak[13] soon published cases which they considered exemplified this transformation. To Hegar's [30] cases we shall have occasion to refer later. Chrobak [13] reported a poly-

pus which he had removed from the fundus of the uterus, which upon microscopical examination presented for the most part the typical structure of a fibroma, with here and there proliferative processes between its connective-tissue fibres. The cells were generally round and a few spindle shaped, and several showed signs of cell division. But from his description they could just as readily have been areas of inflammation; and if they were sarcomatous, no clue was given as to their origin. And Leopold [52] contented himself with stating that there was no doubt that the specimen in his case was a young sarcoma which was due to the "degeneration" of a fibroma. Kunert,[49] in 1875, reported six cases from Spiegelberg's clinic, one of which was a "fibrosarcoma" of the uterine wall, upon the strength of which he stated that it and all similar growths were due to the "degeneration" of fibromata, though he did not attempt to adduce proof in support of his statements. Schröder,[55] in his text book upon the "Diseases of Women," also took a similar position, and in nearly all the subsequent articles both he and Kunert are referred to as having proved that all sarcomata of the uterine wall originate in this way, while in reality they simply expressed their opinion without attempting to prove its correctness. Rogivue,[74] in his dissertation, stated that all parenchymatous sarcomata did not originate in this manner; and Raymond stated that the presence of sarcomatous and myomatous nodules in the same uterus, as in his case, did not necessarily indicate that the former were the result of secondary changes in the latter.

In 1880 A. R. Simpson [85] reported a large sarcomatous growth which he had removed from the interior of the uterus. On section it was perfectly homogeneous and of a light-pinkish color, except for a very few circumscribed myomatous nodules. The homogeneous portion consisted of spindle- and round-cell sarcoma, while the myomatous nodules presented the usual appearance. The growth recurred several times, but in none of the later specimens could any trace of myomatous tissue be found, so he had no hesitation in declaring that the entire growth represented a metamorphosis of a fibromyoma. Jacubusch [33] and Kundrat [48] also described a number of specimens which they considered proved the point in question; but none of them were carefully examined microscopically, and they based their opinions purely upon the macroscopical appearance of the specimens, some portions of which presented the usual

appearance of fibromyomata, while other portions appeared to be sarcomatous. Gusserow,[70] in his article upon sarcoma of the uterus in Billroth-Lücke's "Handbuch der Frauenkrankheiten," stated that sarcomata of the wall of the uterus are usually the result of the "sarcomatous degeneration" of fibromata or myomata, but in a few cases they may be due to a primary sarcomatous infiltration of its parenchyma. The statements of Reunert,[71] who reported three cases from Winckel's clinic in a very careful dissertation, are not much more satisfactory, for, in speaking of the "sarcomatous degeneration" of myomata, he said (page 35): "Perhaps one could also suppose, if one finds at the same time a fibroma and a sarcoma, that the latter tumor was not primarily malignant, but that it represented a degenerated fibroma. In any event this would explain the coexistence of a benign and a malignant new growth in the same organ."

Rothweiler[72] also reported a case in which Schröder performed vaginal hysterectomy. The uterus was as large as an ostrich egg, and from its fundus four polypoid growths, as large as a walnut, protruded into the uterine cavity. One of them was pedunculated and the others sessile; their surface, as well as the endometrium in the upper portion of the uterus, was sarcomatous. Microscopical examination showed that the bases of the polypi were composed of unchanged myomatous tissue, which was continuous with the parenchyma of the uterine wall, but that the portion which projected into the uterine cavity was the seat of a spindle- and round-cell sarcoma. He believed that he had to do with the "sarcomatous degeneration" of myomatous polypi, and considered that he was able to trace the transition from one tissue to the other. His description, however, is not very clear, and, in view of the fact that the rest of the endometrium was likewise sarcomatous, we are inclined to believe that he had to deal with a primary sarcoma of the endometrium which had invaded the surfaces of the submucous polypi, rather than with their "sarcomatous degeneration," somewhat as in our second case. He, however, regarded it as a striking verification of Schröder's view—"ein sprechendes Beispiel für die Schröder'sche Ansicht."

In 1887 Orthmann[73] exhibited before the Berlin Obstetrical Society a sarcomatous uterus which had been removed by Martin, and which was afterward described by Ritter[73] in a dissertation "Ueber das Myosarkom des Uterus." The patient

had noticed the growth for about ten years, when it rapidly became larger and necessitated the supravaginal amputation of the uterus. Recovery from operation; rapid recurrence in the peritoneal cavity; perforation of the abdominal walls by the growth; death six weeks after the operation. In the anterior wall of the uterus was a tumor, twenty centimetres in diameter, which was generally surrounded by a capsule. Upon its anterior surface were two smaller subperitoneal tumors; one, enclosed in a capsule, was a typical fibromyoma, while the other, which was in communication with the large tumor, was a round-cell sarcoma. Portions of the large tumor were distinctly sarcomatous, and other portions presented a typical myomatous structure. Ritter[23] considered the sarcoma the result of "degeneration of the myoma," and stated: In some portions, "between the connective tissue and muscle fibres one finds at first a few small round cells or small collections of cells. They become more and more numerous. Definite cell division may be observed. With the various methods of staining one can trace all its stages up to the formation of double nuclei. Finally we see the fibres pressed apart by masses of cells which occupy nearly the entire field" (page 34). In this case he clearly demonstrated proliferative changes in the interstitial portions of a fibromyoma, and so is in accord with Birch-Hirschfeld,[5] who states that sarcomata are always derived from myomata in this way.

The lymphangiectatic forms of sarcoma which were described by Fehling and Leopold[18] and Fenger[19] were believed by them to have been originally lymphangiectatic fibromyomata which later became converted into sarcomata; but they adduced no histological proof in support of their statements. Bommer,[9] Doran,[15] Dressler,[16] and Behnke[6] have also reported cases which they considered were due to the transformation of fibromyomata into sarcomata; but the microscopical examination showed only the coexistence of myomatous and sarcomatous tissue, without giving any definite information as to the transformation from one to the other.

The latest work upon this subject is that of Von Kahlden,[37] who, in the third case of his recent article, believes that he reports the first case in which the transformation of a fibromyoma into a sarcoma has been definitely proven.

In his case the uterus was 15.5 centimetres in length, with

walls from 2.5 to 3 centimetres in thickness. Its cavity was dilated, and three large, nodular, sessile tumors, which were apparently covered by endometrium, projected into it. The uterine walls were crowded with large numbers of round or oval tumors, up to a hazelnut in size, which are surrounded by capsules. Each tumor is composed of smaller nodules, which generally present a fibrous appearance. In the midst of the fibrous structure of many of the nodules are homogeneous areas. This formation extends from just beneath the mucosa to the outer part of the uterine wall, where it ceases and gives place to a layer of normal uterine musculature.

The microscopical examination showed that the glandular structure of the endometrium was preserved. In the portions of the growth nearest the muscularis he found microscopical nodules, which were surrounded by a thin connective-tissue capsule and sharply marked off from the surrounding tissue. In each of these he found two varieties of cells—one which stains lightly, and another which stains deeply; the former representing muscle, and the latter sarcoma cells. As the cavity of the uterus is approached the nodules become larger and visible to the eye, when they are found to be made up of a number of smaller ones, those nearest to the uterine cavity being frequently composed entirely of sarcoma cells. The tumors which project into the cavity of the uterus are made up of the larger nodules, and in places represent a diffuse sarcoma which has extended into the lower layers of the mucosa.

Von Kahlden [37] considers that this specimen illustrates the very earliest stages in the formation of myoma of the uterus, and that in the very smallest nodules the first stages in the development of sarcoma may be observed. "This occurred in the smallest fibromyoma nodules, by the direct transformation of the muscle cells into roundish and then into short-oval cells which are rounded off at their poles." Nowhere were the muscle and sarcoma cells indiscriminately mixed together, but in each nodule there were definite areas of well-marked sarcoma as well as muscle. And finally he says: "The direct histological proof of the transformation of myoma into sarcoma is here presented for the first time."

After carefully considering Von Kahlden's [37] cases we feel compelled to state that we do not consider that he has really demonstrated that the sarcoma cells were derived from the

muscle cells of the fibromyomata, as he believes. And we are unable to understand from the description of the specimen how he excluded the possibility of the connective tissue which exists between the muscle bundles having given rise to them, or at least having taken part in their formation. Certainly his Fig. 6 does not exclude this possibility, any more than it demonstrates that the sarcoma cells were derived from the muscle cells.

In view of these facts we do not believe that the proof adduced by Von Kahlden in support of the transformation of fibromyomata into sarcomata is at all convincing.

FIG. 1.—Lateral aspect of the tumor from Case 1, one-fourth natural size.

From the preceding review of the work upon this subject it is evident that fibromyomata may be transformed into sarcomata, but the demonstration of the initial histogenetic changes which occur in the process has yet to be adduced.

We shall now pass to the description of our new cases.

CASE I. *Sarcoma-like Myoma of the Uterus* (*Myoma sarcomatodes Uteri*).—Museum specimen No. 4729. From the clinical history, for which we are indebted to the courtesy of Prof. Pibram, we extract the following: Augusta S., admitted to hospital February 4th, 1891; age 47; no children or miscarriages. Menses appeared in the sixteenth year, always regular; menopause four years ago; no loss of blood since. She was perfectly well

up to June, 1890, when she first noticed a gradual enlargement of her abdomen, which increased with great rapidity for the five weeks previous to her admission to the hospital. She did not complain of pain, and was able to go about her work until one week previous to entering the hospital. For the past few weeks there had been marked emaciation and edema of the abdominal walls, legs, and feet. The physical examination revealed no abnormality of the heart, lungs, or kidneys, and showed the abdomen filled by large tumor masses, which were diagnosed as malignant growths arising from the generative tract. Death seven weeks after admission.

Autopsy March 26th, 1891. Anatomical diagnosis: "sarcoma

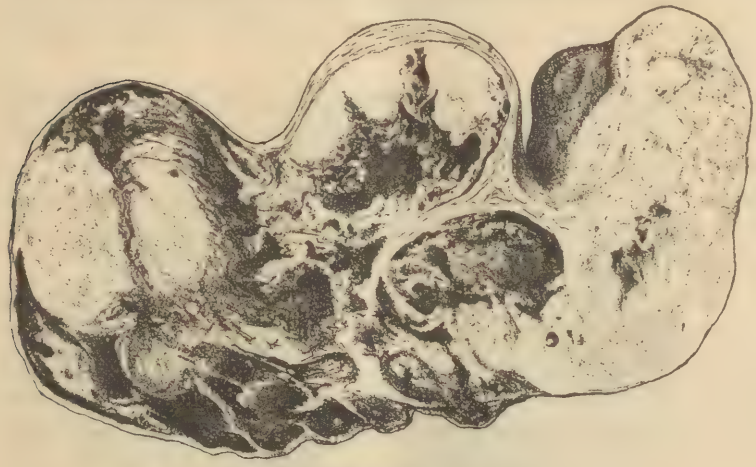

FIG. 2.—Sagittal section of the same.

fuso cellulare uteri (e myomate); morbus Brightii chron.; hydrops et marasmus universalis." Except for the abdominal tumor the autopsy offers little of interest, there being only some old chronic nephritis and old pericardial adhesions. In the abdominal cavity there were over three litres of clear fluid. The intestines were forced into the upper and left portion of the abdominal cavity by a large tumor which entirely filled the pelvis and extended up into the right side of the abdominal cavity, and was adherent to the anterior abdominal wall, the omentum, and surrounding intestines.

The tumor (Fig. 1) measures thirty-six centimetres in its antero-posterior diameter, and is readily divisible into three parts: a central portion, about twelve centimetres in diameter,

which corresponds to the enlarged uterus, from whose anterior and posterior surfaces a large tumor arises, each the size of a man's head. As is seen from Fig. 2, which represents a sagittal section through the entire mass, the anterior tumor arises from the central portion by a thick pedicle, and thus presents a somewhat mushroom-like appearance. The posterior tumor is somewhat larger than the anterior, and is attached by a broad base to the posterior surface of the central portion. Extending from either side of the central portion are the apparently normal tubes and ovaries.

The surface of the central tumor is perfectly smooth, while the others are covered with thin adhesions and are studded with thin-walled cysts of various sizes, with clear or bloody contents, which are more abundant and of larger size in the posterior tumor.

The vagina is greatly increased in length, and from it a sound may be introduced for sixteen centimetres into the uterine cavity, which occupies the left side of the central part of the tumor, thus showing that its greater part was developed in the right wall of the uterus. The uterine cavity is lengthened, but not otherwise increased in size.

A sagittal section through the entire tumor mass (Fig. 2) shows that the anterior portion generally presents a firm, homogeneous appearance, with here and there, particularly toward its anterior border, areas of fibrous structure and small cysts with clear contents; while the other portions present many cysts of varying size, separated by dense grayish-white tissue and alternating with necrotic areas. As is seen from Fig. 2, the upper part of the central tumor mass is surrounded by a layer of unchanged uterine musculature, forming a capsule which in places is over one centimetre in thickness and is readily separated from the underlying tumor. The portions adjoining the capsule are dense and of a firm consistence, while the lower portion is composed of the necrotic areas and cystic formations which characterize the greater part of the growth.

Microscopical Examination.—Small portions were removed from various parts of the tumor and submitted to microscopical examination. Sections through the uterine cavity show that its mucous membrane is atrophic, with comparatively few glands and a slight increase of connective tissue, and presents the typical appearance of the endometrium after the meno-

ERRATUM.

The description under figure 3, page 27, should go under figure 4 on page 28, and vice versa.

pause. It is surrounded on all sides by unchanged muscularis, and it is only at a distance of a centimetre or more from its right margin that the sarcomatous growth makes its appearance. A casual examination of sections from various parts of the growth shows that we have to deal with a spindle-cell tumor with many necrotic areas; but a more careful examination shows that it presents many points of interest and gives us important information as to its mode of origin.

Sections through the upper part of the central tumor mass

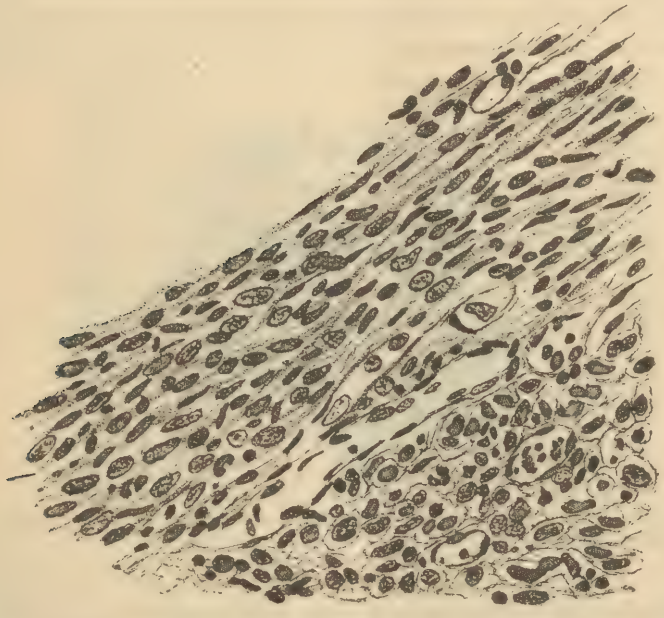

FIG. 3.—Sarcomatous portion from the anterior portion of the same tumor, showing giant cells and reticulum. Zeiss Oc. 2, Obj. E.

show that the capsule is composed of perfectly normal uterine musculature, and the superficial portions of the tumor beneath it present for the most part the appearance of a myoma, with here and there sarcomatous areas scattered through it. The sarcomatous structure becomes more evident as we approach the central part of the tumor, where we find the large, necrotic areas and cystic formations. The sarcomatous tissue is composed of large spindle cells, which are thickly crowded together, with here and there large giant cells with from two to six or eight central nuclei. Where the cells are not too closely crowded

together we see that they are separated by a small amount of connective tissue (Fig. 3). The growth contains many vessels, the walls of many of the arteries presenting marked hyaline degeneration.

As the capsule is approached the cells become less crowded together, and gradually myomatous tissue appears. In places it appears quite probable that the sarcoma cells are derived from those of the myoma. For in some portions of the growth we see apparently perfectly normal muscle cells: then their nuclei become larger, some attaining two or three times their normal size, while in others karyokinetic figures are observed. Then the cells become greatly increased in number and much more closely crowded together, and the tissue assumes a dis-

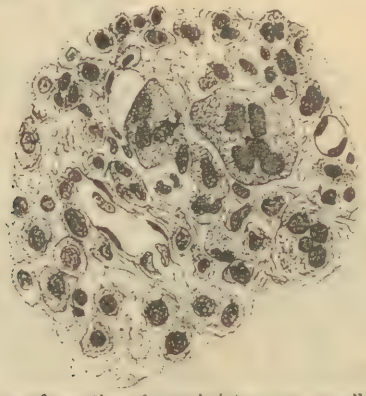

FIG. 4.—Showing the transformation of muscle into sarcoma cells, from the median portion of the tumor. Zeiss Oc. 2, Obj. E

tinctly sarcomatous appearance. The connective tissue which is between the muscle cells is seen to be continuous with that between the sarcoma cells. Fig. 3 gives a fair idea of this change. In its lower right-hand corner we see perfectly typical spindle-cell sarcoma with many vessels and marked intercellular substance, while in the upper right-hand portion of the figure we see apparently normal muscle cells with long (*stäbchenformig*) spindle-shaped nuclei; then the nuclei become larger and more oval, and the cells gradually increase in number, so that at last at one end of the field we see a typical spindle-cell sarcoma, while at the other we have apparently normal muscle.

While the examination of portions from the central tumor renders it probable that the sarcoma cells are derived from the muscle cells, this mode of origin is rendered absolutely certain

upon the study of sections from the anterior tumor. A short distance from the surface the growth presents the typical structure of a spindle- and giant-cell sarcoma (Fig. 4). Here we see large spindle and giant cells separated by a large amount of intercellular substance with many vessels. Immediately adjoining this, however, are areas in which the sarcomatous structure is not so well marked, and adjoining them areas in which we find only typical myomatous tissue. But in many places the transition is so gradual that it is absolutely impossible to say where the muscular tissue ends and the sarcomatous begins, and we only feel sure of ourselves when we are at one or other end of the process; and even in the otherwise normal myomatous

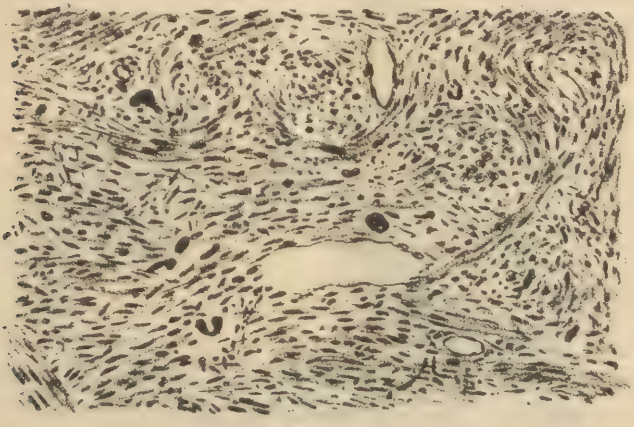

FIG. 5.—Myomatous tissue with enlarged cells and nuclei scattered through it, from the anterior portion of the same tumor. Zeiss Oc. 4, Obj. AA.

tissue we find some of the cells increased in size, and here and there a giant cell or a karyokinetic figure.

Fig. 5 represents a section from near the surface of the anterior tumor under a low power; and it is evident that here we have to deal with myomatous tissue, the only regard in which it differs from perfectly normal myomatous tissue being the presence of very large, deeply staining bodies, of various size and frequently of bizarre form, which are scattered through it. Fig. 6 represents an area from the above Fig. 5, more highly magnified. In its centre we see a large space lined by endothelial cells, from whose upper end extends a small capillary which contains several leucocytes. The surrounding tissue is composed of typical long, spindle-shaped muscle cells

which are separated by a considerable amount of connective tissue. Scattered through the section are large cells with nuclei of various sizes and shapes, some being hardly larger than the muscle cells, while others are five or six times as large. Several of them contain large vacuoles; in others the large nucleus appears to be going to break down into several smaller ones; and in others (not represented in the drawing) we find several smaller nuclei in a single cell body—in other words, typical giant cells. In some of the smaller cells karyokinetic figures are also observed. Accordingly there can be no doubt that the great part of the growth, spindle as well as giant cells, is derived from the muscle cells of a primary fibromyoma, while its connective-tissue elements do not appear to be involved in the process.

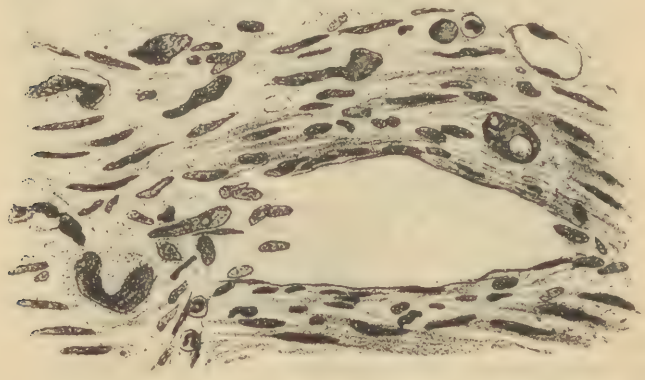

FIG. 6.—A portion of Fig. 2 more highly magnified. Zeiss Oc. 2, Obj. E.

Our specimen, judging from the history and microscopical appearance, was apparently originally a fibromyoma of the uterus, composed of a single interstitial and two larger subperitoneal nodules, which at a later period underwent the changes which we have just described. It accordingly represents the transformation of a primary fibromyoma into a sarcoma-like growth by the proliferation of its muscle cells, and presents a marked contrast to the case in which Von Kahlden[5] attempted to demonstrate a similar mode of origin, for in it he found only sarcoma cells adjoining muscle cells, but failed to demonstrate the transition of one to the other; and the fact that the sarcoma cells are not scattered through the smallest myoma nodules, but are grouped together and sharply marked off from

the adjacent muscle cells, speaks against such a mode of origin, instead of for it as he believes. And it is the converse of Ritter's [73] case, in which the sarcoma was in all probability the result of the proliferation of the connective-tissue elements of the myoma.

As the new growth in our case was derived from a proliferation of the muscle cells and not from the connective tissue, the question naturally arises, Are we entitled to class it among the sarcomata?

While there is no doubt that connective tissue and muscle cells are both of mesoblastic origin and consequently more or less closely related, there is equally no doubt that they represent essentially distinct tissues; and *a priori* we should hardly be justified in classing non-striated muscle among the connective-tissue elements, as we should be obliged to do were we to designate the growth before us as a sarcoma.

For these reasons, when we first became acquainted with the nature of our tumor, we sought to designate it by some term which would indicate its muscular origin and at the same time keep it distinct from the sarcomata, and we thought of calling it a malignant myoma, "myoma malignum," thereby briefly stating its origin and its malignant, proliferative properties; but upon further consideration we concluded to designate it as a "sarcoma-like myoma," or "myoma sarcomatodes," thereby expressing its relationship to both the myomata and sarcomata.

We do not consider this term as at all synonymous with the term myo-sarcoma. The former, we believe, indicates a sarcoma-like tumor derived from the muscle cells of a myoma; while the latter, according to the somewhat loose terminology in vogue among the sarcomata, only indicates a mixture of sarcomatous and muscular tissue and has no reference to its origin.

In connection with our specimen of "myoma sarcomatodes," two cases described by Pestalozza [65] as infectious hemorrhagic sarcoma of the uterus are of great interest, for in them he believed that he observed changes in the muscle cells more or less similar to those in our specimen. He described small hemorrhagic growths arising from the fundus of the uterus in two women, aged respectively 25 and 33 years, which rapidly led to death—in one case within six months—with hemorrhagic metastases in the lungs and vagina. The uterine tumor in each case was a round-cell sarcoma, which contained large numbers of

giant cells with usually not more than two nuclei. He believed that the giant cells were derived from the muscle cells of the parenchyma of the uterus, and in his Fig. 7 gave a drawing, illustrating the process, which is quite similar to our Fig. 4. He also found giant cells in the muscularis some distance from the sarcomatous growth, just as in our case; and in several instances they could be found making their way into the vessels or already within them, which readily explains the formation of metastases.

It is not clear from his description to what the round cells, which make up the greater part of the growth, owe their origin. He was inclined to believe that they were connected in some way with the decidua and were probably closely related to the decidual-cell sarcomata. After carefully considering his cases we believe that they are decidual-cell sarcomata, and the muscle changes, if they really occur, play only an insignificant part in the production of the growths.

Beissheim,[7] a pupil of Rindfleisch, has also attempted to show that sarcomata may arise from the muscle cells. But his statements are based mostly upon theoretical considerations as to the relation between muscle and connective tissue, and the specimen which he adduces in their support does not appear convincing; but after our own experience we do not wish to deny that he observed such changes.

It is quite probable that Hegar[30] observed structures similar to those described by Pestalozza[65] and ourselves, for in his article upon sarcoma of the uterus he reported a case (Case 8) in which he had removed a tumor weighing two pounds from the uterus of a woman aged 44 years. Fifteen months later there was a recurrence, the second growth exceeding the first in size. The first growth he considered a fibromyoma, and the examination of the second by R. Maier showed that it was a fibromyoma which differed in only one particular from the normal: "Als auffällig und nicht gewöhnlich ist nur ein Verhalten zu bemerken. Es finden sich an einzelnen Stellen und an diesen dann gewöhnlich zahlreich mitten in dem Zuge der Fasermassen und parallel mit diesen spindelförmige grosse Figuren, wie ungeheuer vergrösserte Spindelzellen. Sie hatten die grösste Aehnlichkeit mit den oft zu förmlichen Brutschläuchen umgewandelten Zellen des Bindegewebes bei lebhaften Proliferations processen oder bei Umwandlung von Bindegewebe in Knorpelgewebe. Die

Räume sind gefüllt mit einer Masse von Kernen, Körnern, Fettmolekülen. Sie sind oft ziemlich lang, 0.04 millimetre, und breit 0.0047." [1]

From the consideration of our case and the work of our predecessors, it is evident that fibromyomata may be transformed into sarcomata either by the proliferation of the connective-tissue cells between the muscle bundles (Ritter), or by the proliferation of the muscle cells themselves, or possibly by a combination of both processes, the first giving rise to ordinary sarcomata and the second to muscle-cell sarcomata.

In connection with the consideration of the "sarcomatous degeneration" of fibromyomata, our second case is of considerable interest—namely, a sarcoma of the endometrium which has invaded the surface of several interstitial myomata. Similar cases have been regarded by Rothweiler [77] and others as demonstrating the transformation of myoma into sarcoma. We, however, regard the two processes as absolutely distinct, and consider the involvement of the myoma as purely accidental, it being entirely due to its situation just beneath the endometrium. Similar cases have been described by Martin,[54] Dressler,[16] and others.

The case of Raymond [69] and the first case of Von Kahlden, in which there was sarcoma of the endometrium with myomatous nodules in the uterine wall, and the case of Gottschalk,[23] in which a subperitoneal myoma was associated with sarcoma of the endometrium, all serve to demonstrate that the involvement of the myoma in such cases is absolutely dependent upon its situation, and not upon any connection between the two processes.

Case II. *Sarcoma Mucosæ Uteri et Myomata Uteri.*—Museum specimen No. 3381. Marie Z., age 52 years; no clinical history. Anatomical diagnosis: "Sarcoma uteri gangrenosum; ulcera necrotica in vagina; urocystitis catarrhalis; pyelonephri-

[1] As remarkable and uncommon only one peculiarity is to be noted. There are found in a few places, in the centre of the fibrous stroma and parallel with it, numerous large spindle-shaped bodies resembling immensely magnified spindle cells. These had a marked resemblance to those connective-tissue cells which sometimes change into regular breeding places (Brutschläuchen) at the time of active proliferation or during the transformation stage of connective tissue into cartilage. The interstices are filled with nuclei, granular masses, and fat molecules. They are sometimes quite long, 0.04 millimetre; their width is 0.0047.

tis lateris utriusque; pneumonia lateris dextri; septicemia; marasmus."

The vagina was 9.5 centimetres long. Its upper portion was smooth and of a dark color mottled with whitish spots, while its lower half was of a bluish-violet color. At the posterior commissure was an ulcer, 2.5 centimetres in diameter, with sharp margins and a shallow, yellowish base. Around it were several smaller ulcers, and at one side a prominence 5 by 3 millimetres arose.

The uterus measured 14.5 centimetres from the external os to the fundus, its greatest breadth being 11 centimetres. Under its serosa, near the attachment of the left tube, was a small nodule the size of a bean. At the fundus the uterine wall was 1 centimetre thick, its lower portion being of various thickness; for a nodular fibroid (?) tumor, 4 centimetres in diameter, occupied its anterior wall and extended down as far as the os internum. The surface of the tumor projected into the uterine cavity and presented a jagged, irregular, ulcerated appearance. The rest of the uterine cavity showed no trace of its normal mucous membrane, but presented an irregular, villous, necrotic surface, which was composed of a soft tissue rich in vessels, and which apparently extended down into the muscularis. In the centre of the posterior wall was another nodule, the size of a hazelnut, which appeared to be a fibroid. The cervix was intact, 3.5 centimetres long, and its walls 0.8 centimetre in thickness. The tubes and ovaries were normal.

Microscopical Examination.—Sections from various parts of the specimen clearly show that the sarcomatous new growth is limited to the inner surface of the uterus and extends only a short distance into its walls. It is probable that it originated in the mucosa, but, as no trace of the endometrium remains, positive proof for this mode of origin cannot be adduced.

Sections through the upper part of the large myomatous nodule and the adjacent portions of the uterine wall and cavity show clearly that the growth did not originate in the myoma, but only involved the portions of it which were adjacent to the uterine cavity, just as it did the other portions of the uterine wall.

The growth is a spindle- and round-cell sarcoma, which contains some giant cells and very few vessels, and is entirely limited to the inner surface of the uterus. In general its most

internal portions are necrotic and present nothing but cellular débris and the remains of nuclei. A little further removed from the interior of the uterus the tissue is well preserved and consists of spindle and round cells, closely packed together, with a very small amount of intercellular substance. The smallest cells are hardly larger than leucocytes. In many portions small bands of non-striated muscle may be seen scattered through it, which increase in number and size as the exterior of the uterus is approached, until at last we come to well-marked muscular tissue with only a few sarcoma cells scattered between its fibres, beyond which the uterine wall presents its normal appearance.

From the study of the specimen it is readily seen that the growth is invading the uterine walls from within outward, and in its course affects the myomata which happen to be in the uterine wall, as well as the perfectly normal uterine tissue.

The various myomatous nodules, where they are not invaded by the sarcoma, present the typical microscopical appearance and contain many areas of myxomatous degeneration.

And, finally, we desire to describe the following unique case of melano-sarcoma of the uterus:

Case III. *Melano-sarcoma Corporis et Cervicis Uteri.*—Museum specimen No. 2717. R., aged 60 years; no clinical history. Anatomical diagnosis: "Melano-sarcoma uteri; sarcomata metastatica cerebri; marasmus; edema pulmonum." From the autopsy records we extract the following: "Dura mater pale; pia mater contains a considerable amount of serous effusion. Brain substance soft, doughy; cortex pale brown; medullary substance yellowish-white in color, with many blood points scattered through it. Scattered through both the superficial and deep portions of the cortex are numerous blackish nodules which are composed of a soft tissue."

The lungs normal except for edema. Heart normal except for a small excrescence upon one of the semilunar valves. Other organs normal.

The uterus is converted into a tumor the size of a head. The cervical region was preserved and markedly dilated, and the cavity which resulted was filled by a collection of thick fluid. The anterior lip of the cervix was converted into a tumor the size of an orange. The tubes and ovaries were normal, and the lymphatic glands of the neighborhood were enlarged.

We shall now describe the specimen, which had been preserved

for some years in alcohol. The uterus has been cut open from its anterior surface, and, generally speaking, has an hour-glass shape, which is due to the presence of tumor masses in its fundus and cervix, while the intervening portion of its body remains intact. From the fundus to the lower margin of the cervical new growth the uterus measures seventeen centimetres, its greatest antero-posterior thickness being seven centimetres. The fundus is occupied by an irregularly-shaped tumor mass which completely fills the upper part of the uterus and extends downward for a distance of eight centimetres. It is generally of a dark color, in some portions being almost black and in others lighter in color. It is dense on section and presents a striated appearance. The tumor is very intimately connected with the uterine walls, but the distinction between it and the uninvolved musculature is very marked. The muscularis is most invaded at the fundus, where it does not exceed one millimetre in thickness; it then gradually increases in thickness, until at the lower margin of the new growth it measures one centimetre.

The entire cervical region is transformed into an irregular, globular mass, about seven centimetres in diameter, which has the same general appearance as the tumor in the fundus, but is of a lighter color. It protrudes into the vagina, but does not involve its walls; no trace of the cervical canal can be found within it; and as with the tumor in the fundus, so here, the distinction between the new growth and the muscularis is very marked. The fundal and cervical tumors are separated from one another by an area of perfectly intact uterine wall, which in its narrowest part has a vertical diameter of three centimetres. Upon the inner surface of this area there are numerous small depressions, the largest not exceeding one millimetre in diameter, which represent the openings of the uterine glands. From this a portion of the endometrium may be traced upward and be found to cover a considerable portion of the lower surface of the fundal new growth. The intact portions of the uterine wall vary from four to ten millimetres in thickness. The vagina is wide and smooth, and appears to be perfectly normal. The tubes are normal, and the ovaries small and atrophic.

Microscopical Examination.—Sections through the fundal tumor and the underlying portions of the uterine wall show that the tumor is sharply marked off from the uninvolved portions of the muscularis by a slight line of small-cell infiltration. The

most superficial portions of the tumor are necrotic, and nothing can be distinguished in it save fragmented nuclei and granular débris. In its deeper portions the structure is well preserved, and it is seen that it is composed for the most part of large spindle cells with very deeply staining nuclei. These cells vary considerably in size, but the smallest are at least twice the size of polynuclear leucocytes. In some portions of the tumor large numbers of giant cells are observed, which are of varying size and possess from one to eight or ten central nuclei. Occasionally they are so abundant that fifteen or twenty may be counted in a single field under the high power, while in other places it is necessary to search through several fields before finding one. Many of the cells, spindle as well as giant cells, are filled with yellowish-brown pigment granules, to which the growth owes its dark color. In some of the cells karyokinetic figures may be observed. As the muscularis is approached, bands of unchanged muscular tissue may be seen extending up into the tumor, and throughout its greater part very small bands of muscle may be found, indicating its invasion by the new growth. The tumor from the cervical region presents identically the same structure as that from the fundus. In no part of the tumor are there large quantities of blood vessels.

Sections through the uninvolved portions of the uterine wall show that its muscularis is perfectly normal and that very little is left of the endometrium. There is no trace of its superficial epithelium; there is some small-cell infiltration, and here and there small cavities which are lined by a single layer of cuboidal epithelium, and which represent all that is left of the glandular structure of the endometrium. The tissue is not well enough preserved to permit us to make any definite statements as to the probable histogenesis of the tumor.

As far as we can learn, this is the only well-authenticated case of melano-sarcoma of the uterus which has been recorded; for, while several cases may be found in the literature which may possibly belong among them, this is the only one which has presented the typical macroscopical appearance of a melano-sarcoma, and, after careful microscopical examination, been described as such.

We have been able to find in the literature only three references to this class of growths, and, as will be seen, none of them present the characteristics of the melano-sarcomata to the same

degree as our case, even admitting that they were melano-sarcomata, which appears more than doubtful.

It is probable that some of the cases referred to by Klob[45] as carcinoma melanodes, or "Pigmentkrebs," may belong in this category; but he stated that, as far as he knew, a primary case of melano-carcinoma of the uterus had never been described, and that "I know also of a case, observed in Rokitansky's Anatomical Institute in Vienna, of diffuse carcinoma melanodes in a markedly enlarged uterus, with a similar growth in both ovaries."

It is quite probable that this case was similar to our own, but in view of its scanty description we are not justified in stating that it was a melano-sarcoma.

The next reference in this connection is a case which G. W. Johnston[35] reported as a melano-sarcoma of the cervix uteri. He removed from a negress, aged 40 years, a pear-shaped polypus, three-quarters of an inch in its greatest diameter, which arose from the cervical canal just above the os externum by a pedicle 1.5 inches long and as thick as a lead pencil. "The tumor was pear-shaped, with a smooth, glistening outer surface; it was hollow and contained about half a drachm of greenish-yellow fluid."

The tumor was examined by Dr. Gray, of the Army Medical Museum in Washington, who made the following report: "The outer surface is covered by a squamous epithelial mucous membrane, the central cavity being lined by a ciliated, columnar epithelium. The mass of the tumor is composed of large spindle cells and very delicate connective-tissue fibres, which in places form alveoli containing small round cells whose protoplasm is entirely obscured by pigment. In the neighborhood of the alveolar structures the blood vessels are in an embryonic state, in other places better developed, but nowhere are seen perfectly formed blood vessels. The tumor also exhibits a tendency to cystic degeneration; several of the cysts are lined by columnar epithelium, and the cavities filled by a finely granular mass containing a few epithelial cells. I would designate the specimen as one of melanotic alveolar sarcoma or of endothelial cancer undergoing cystic degeneration."

From the above description it is evident that the polypus in question cannot be compared with ours, and that even its sarcomatous nature is open to doubt.

The only other reference in this connection is to be found in

a dissertation by Seeger[67] (1891), in which he reports five cases of sarcoma of the uterus from Gusserow's clinic. It is probable that his fourth case may belong in this category, though he does not describe it as a melano-sarcoma. Gusserow performed supravaginal amputation of the uterus in a woman aged 50 years. "The microscopical examination of the tumor shows areas rich in cells, with little intercellular substance alongside of fibrous portions, the cells exhibiting all possible gradations, from smaller and larger spindle cells to distinct giant cells with many nuclei and occasionally of a branching shape. *Many cells contain a finely granular pigment*, here and there fatty degeneration, but not marked enough to lead to softening."

The consideration of the references just adduced renders evident our statement that our Case 3 is the only well-described case of melano-sarcoma of the uterus which has as yet been recorded.

A point of considerable interest, in connection with the three cases which we have just described, is that they all contained considerable numbers of giant cells with from two or three to eight or ten central nuclei. Occasionally as many as fifteen or twenty giant cells might be counted under a single field of the microscope, under others only a few, and sometimes it was necessary to search through several fields to find a single one.

In view of their comparative abundance, however, in our cases, it is surprising to find that Rheinstein,[72] in describing his case of "giant-cell sarcoma of the endometrium," stated that he was the first to have observed giant cells in sarcoma of the uterus, and that Von Kahlden[37] stated that they had been noted very rarely, and, with the exception of his case, had only been observed by Ahlfeld[2] and Rheinstein.[72]

On the other hand, exclusive of our cases we have found at least *eleven* other cases of sarcoma of the uterus[2] in which giant cells had been described previous to the appearance of Von Kahlden's[37] article, and several others since then. Besides the two cases of Pestalozza[65] and the cases of Hegar[30] and Seeger,[67] to which we have already referred, giant cells were found in four cases of Terillon[94] and in one of Katz,[39] not to mention the cases of Ahlfeld[2] and Rheinstein,[72] to which Von Kahlden[37] referred. Giant cells were also described recently by Coleman[14] in a case of sarcoma of the endometrium.

Strange to say, Sänger[50] is the only observer who mentions

their presence in the decidual-cell sarcomata, where one would naturally expect to find them. They were likewise observed in a case recently operated upon by Dr. Menge in the Leipzig Frauenklinik, the specimens from which he kindly allowed us to examine. We suppose that they occurred likewise in most of the other cases, but failed to be mentioned by the various observers.

It is evident, however, from our experience and from the facts which we have gleaned from the literature, that they occur much more frequently than is generally supposed; and now that we have directed attention to their more frequent occurrence, they should no longer be regarded as rarities and will be mentioned more frequently.

In conclusion, we desire to express our thanks to Prof. Chiari for the material upon which this article is based, and especially for his kindness in supervising our work. We also desire to express our indebtedness to Prof. Sänger, of Leipzig, for the use of his library, which he very kindly placed at our disposal.

LEIPZIG, March 15th, 1894.

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